

ADVANCES IN LLM

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New Concepts in Treatment Approaches and Prognostic Factors in Aggressive NHL

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H&O What is the definition of aggressive non-Hodgkin lymphoma?

MS “Aggressive” is defined by the natural history of the disease if it were to remain untreated. The cells multiply rapidly and quickly lead to fatal disease. However, although aggressive non-Hodgkin lymphoma (NHL) can be fatal if not treated, a subset of patients can be cured with standard therapy.

H&O What are the various types of aggressive B-cell and T-cell lymphomas?

MS Among the aggressive lymphomas, the most common subtype is diffuse large B-cell lymphoma (DLBCL), comprising approximately 35–40% of all adult lymphomas. Others include Burkitt lymphoma and mantle cell lymphoma, which has been recognized as a distinctive disease for only 5–10 years; these are more rare and are treated similarly to leukemias.

T-cell lymphomas are also very heterogeneous, and are quite rare, accounting for less than 10% of all lymphomas. The classification of these subtypes is still ongoing.

H&O How does the heterogeneity of the subtypes of aggressive NHL affect therapeutic research?

MS It is important to consider the heterogeneity within the term “aggressive NHL” since there are a number of different lymphomas that fall into this category. The biology

of these lymphomas is somewhat different, and therefore the outcomes with current treatments are also different. The varying biology of the different subtypes also means that strategies to improve therapy would vary.

One of the most obvious examples of this concept is that aggressive NHL includes several types of B-cell lymphomas, which arise from specific types of normal B lymphocytes, and several types of T-cell lymphomas, arising from specific types of normal T lymphocytes. Among the most potent new agents being used to treat lymphomas is an antibody directed against a protein expressed in B-cell but not T-cell lymphomas. Without distinguishing between subtypes it would be impossible to determine which types of lymphoma to treat with an antibody directed to a protein present only in B-cell disease.

Also, because many of the subtypes are relatively uncommon, it is difficult to conduct large clinical trials. Accruing the number of patients necessary to conduct a rigorous study is very challenging for these rare subtypes.

H&O Is it possible to combine subtypes into a single clinical trial, even though the biology of each subtype might be somewhat different?

MS This approach has been tried; however, if the diseases are different in their biology such a study may not yield the same clues about treatment as if only a single disease were considered. The history of the treatment of mantle cell lymphoma provides a useful example here. As mentioned above, until recently mantle cell lymphoma was not considered a distinctive disease and was included in large trials of aggressive B-cell lymphomas and other diseases. Not until it was appreciated as a separate entity could treatment responses be evaluated properly for patients with this disease. The natural history of mantle cell lymphoma is different from other B-cell lymphomas. Early limited data now suggest that certain new agents may be particularly beneficial for mantle cell lymphoma, which would not have been known if it were not recognized as a distinct subtype. Future clinical trials need to be targeted toward specific diseases rather than a broad category of tumors.

H&O In what ways are considerations about the biology of lymphomas changing?

MS Advances in our understanding about the molecular nature of aggressive lymphoma are changing the way we consider its biology. As an example, the way that we think about the biology of DLBCL is undergoing a change. One of the standard ways of thinking about DLBCL was in terms of a clinical prognostic factor scheme. If some common clinical features among patients presenting with the disease could be identified, then, based on the number of these features present at diagnosis, it would be possible to determine the likely outcome of a given patient after treatment with standard chemotherapy. Now, investigators are seeking to improve the precision of such analyses using molecular prognostic factors and molecular insights into the disease. The use of molecular prognostic factors does not replace clinical prognostic factors, but does improve our ability to assess patients with various aggressive NHL subtypes.

H&O How has the treatment of DLBCL changed in recent years?

MS The therapeutic advancement that has been most important in the treatment of DLBCL is the addition of the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec) to standard chemotherapy. For years, DLBCL was treated with the combination chemotherapy regimen known as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Investigators had attempted to improve outcomes of patients using minor variations in this regimen, modifying the way in which the agents were administered, and adding other chemotherapeutic agents to this core backbone. However, none of these minor modifications significantly altered patient outcomes. Over the past several years, clinical trials have shown clear evidence that adding rituximab to CHOP improves both the complete response rate and the durability of responses, and appears to be associated with a higher cure rate. Now, virtually all patients with DLBCL are treated with CHOP plus rituximab as their initial therapy. Ongoing studies are evaluating rituximab as consolidation therapy, in association with treatments at a later time point in patients who relapse, and in association with a transplant regimen.

H&O Has rituximab been integrated into the treatment of other B-cell lymphoma subtypes?

MS Yes. The largest studies so far have been in DLBCL and follicular lymphoma, the most common indolent B-cell lymphoma. Smaller ongoing studies are evaluating rituximab in the treatment of Burkitt lymphoma

and mantle cell lymphoma. This antibody is particularly suited for the treatment of B-cell malignancies because the majority of these diseases express CD20, the protein against which rituximab is directed, on the cell surface.

H&O How has the success of rituximab changed considerations about B-cell lymphomas?

MS Interestingly, the results obtained in studies with rituximab have changed our considerations about what constitutes low- or high-risk disease. The addition of rituximab into the treatment regimen has led to improved outcomes in subsets of patients that had been traditionally thought of as having very high-risk disease. In the bigger picture, these changes point to the need to revise the criteria being used to identify high- and low-risk patients.

As an example, investigators had identified certain molecular features of tumors cells that rendered them more or less responsive to chemotherapy; one aspect that seemed to be associated with outcome was “cell of origin,” similarities between tumor cells and specific normal B cells. According to research findings, tumors that resemble normal germinal-center B cells appear to be associated with a more favorable outcome with standard chemotherapy compared with tumors without any features related to normal germinal-center B cells. With the addition of rituximab, the predictive value of molecular classifications based on the relationship to normal types of B cells are not nearly as striking.

H&O In what ways are the criteria being revised?

MS There are a couple of different ways in which the criteria can be revised. First, patients can be analyzed in a similar way to that done years ago for patients treated with CHOP-like regimens. Through gathering data on the features most closely associated with good and poor outcomes among patients treated with CHOP plus rituximab, a new set of clinical prognostic factors can be developed.

The definition of what constitutes a prognostic factor has changed somewhat over the past few years. The clinical characteristics of a patient at the time of presentation reflect the aggressiveness of the disease, but they do not provide information about why a particular disease grew rapidly or was less sensitive to chemotherapy. There has been increasing interest in understanding at a molecular level why one tumor responds to therapy and another does not. Another reason for the increasing focus on molecular prognostic factors is that as therapeutic research moves increasingly toward rational targeted therapy, it is very important to know which tumors might express a particular target and in which tumors that target might be deregulated.

With the sequencing of the human genome and technical advances that enable us to screen tumors for the expression of any gene in the body, it is possible to develop comprehensive profiles of tumors and to ask specific questions about characteristics that might be associated with differences in outcome. For example, this approach has enabled identification of features that relate tumors to different stages of normal B-cell differentiation, and correlation between tumors in the various categories with differences in outcome.

H&O How are gene expression profiles used in the identification of molecular prognostic factors?

MS Gene expression profiles can be used to compare the molecular signature of tumors from patients who were cured and from patients who were not cured. If the differences between these two signatures could be understood, it might enable identification of specific pathways that might be promising rational targets.

Earlier studies were limited by the fact that patients who were identified as not doing well on therapy were simply treated with more standard chemotherapy. We did not identify why they did not do well and shape subsequent treatment accordingly. Understanding specific pathways and the biology behind specific tumor types can lead to the development of more effective targeted treatment.

H&O How else are molecular signatures being used in aggressive NHL?

MS Mediastinal large B-cell lymphoma has always been treated like DLBCL, although there are some specific clinical features that differentiate the former from the latter; for example, mediastinal large B-cell lymphoma occurs primarily in young women and as localized disease, neither of which is a feature of DLBCL.

Using the molecular signature of primary mediastinal large B-cell lymphoma, a couple of studies have found that this disease looks similar to Hodgkin lymphoma. These two tumors behave somewhat similarly. This finding has prompted clinical investigators to begin to think about how this information might impact the treatment of mediastinal large B-cell lymphoma.

Also, new information from molecular platform techniques indicates that there may be subtypes of lymphomas that have not been previously recognized. There appear to be differences in biology and, most likely, in some of the genetic lesions that cause these lymphomas that were not previously appreciated. Hopefully, this information will lead to the development of more precise therapy.

H&O Have similar major advances occurred with the T-cell subtypes of aggressive NHL?

MS With T-cell lymphomas, there have not been such significant changes in treatment over the past few years. Although antibodies directed against proteins on normal T cells and T-cell lymphomas exist, there is no equivalent to rituximab in terms of an agent dramatically improving outcomes. One of the major challenges over the next few years will be to use new insights into the basic biology of T-cell lymphomas to advance treatment. The aggressive T-cell lymphomas tend to have less favorable outcomes than the aggressive B-cell lymphomas, and a great deal of improvement is needed in therapeutic options.

Suggested Reading

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